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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,472	03/29/2002	Eric Lam	RU-0170	3041

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EXAMINER
RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,472	LAM ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- *The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *10-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 May 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-20 are currently at issue and are present for examination. Claims 1-9 are now under consideration. Claims 10-20 remain withdrawn from consideration as being drawn to non-elected invention.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-9, in Paper No. 7 is acknowledged. The traversal is on the ground(s) that all of the claims of the present invention share the same technical feature as being related to detection of the presence or activity of a predetermined protease and the restriction requirement fails to meet the criteria for proper restriction under both PCT Rule 13.1 and 13.2. This is not found persuasive because Examiner can find lack of unity if prior art teaches the invention of the first claim. According to 37 CFR 1.475, "Unity of invention before the International Searching Authority, the International Preliminary Examining Authority and during the national stage, (a) An international and a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. Where a group of inventions is claimed in an application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features". The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. (See also 37CFR 1.475 (b-e). In the instant case, prior art teaches method of detection of protease activity using chimeric constructs comprising a reporter and a repressor, the invention of claim 1 (see for example, Dasmahapatra et al. US

5599906, 2-14-1997). Thus, the invention when considered as a whole, does not contribute over the prior art.

The requirement is still deemed proper and is therefore made FINAL.

Claims 10-20 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 7.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. For example, applicants do not provide SEQ ID NO to sequences recited in some figures. See particularly 37 CFR 1.821(d).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chimeric protein comprising a ß-glucuronidase linked to a hormone binding domain by a peptide comprising a spacer sequence and a caspase cleavage site wherein the ß-glucuronidase is inactive due to the linkage to the hormone domain and the release of the ß-glucuronidase through caspase cleavage of the cleavage site restores the enzyme activity of ß-glucuronidase, does not reasonably provide enablement for such fusion protein comprising any reporter and any repressor linked through a protease (caspase) cleavage sequence or such fusion proteins comprising plurality of reporter and repressor domain linked by more than one type of caspase cleavage linkers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1 and 4-8 are so broad as to encompass fusion proteins comprising any reporter and repressor. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of such fusion proteins broadly encompassed by the claims. Applicants invention is such that one of skilled in the art needs to

be taught as to what are the repressors for any selected reporter molecules. For example while the specification teaches that a hormone binding domain of a steroid hormone receptor can act as a repressor of a ß-glucuronidase, the specification is totally silent as to the repressors for all or any other type of enzyme that those skilled in the art would choose. Since there is no such teaching in the specification it would require undue experimentation of the skilled artisan to make and use the very broadly claimed chimeric polypeptides. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While a large number of reporter molecules are known along with recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple repressors that can be used in a fusion protein to repress the said reporter as encompassed by the instant claims. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass fusion proteins comprising any protein as reporter and repressor because the specification does not establish: (A) a universal list of all the reporters (for example, all enzymes) and their specific repressors; and (B) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including fusion protein comprising any reporter and any repressor. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of chimeric polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 1, 4-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 4-8 are directed to chimeric polypeptides comprising any reporter and repressor. Claims 1, 4-8 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides including modified polypeptide sequences, that have not been disclosed in the specification. No information, beyond the characterization of the function (ß-glucuronidase and its repressor, hormone binding domain) of a single species has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure and function of all the polypeptide sequences, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can

have a wide variety of functions and with the potentiality of generating many different antibodies. Therefore many structurally and functionally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-5 are rejected under 35 U.S.C. 102(a) as being anticipated by Hawkins et al. (PNAS, Vol. 96:2885-2890, March 1999). This rejection is based upon the public availability of a printed publication before the filing date of the instant application. Claims 1 and 4-5 of the instant application are drawn to a chimeric protein for detecting the presence of predetermined protease, comprising a repressor domain which represses the activity of a normally biologically

active protein fused thereto as a reporter domain having a detectable activity when not fused to the repressor domain, both of which are linked together through a linking sequence comprising a protease cleavage domain of the predetermined protease, wherein the protease cleavage domain comprises a cleavage site for a caspase, wherein the linker sequence comprises spacers in between the repressor or reporter and protease cleavage site. Hawkins et al. disclose an identical chimeric protein comprising a repressor domain which represses the activity of a normally biologically active protein fused thereto as a reporter domain having a detectable activity when not fused to the repressor domain, both of which are linked together through a linking sequence comprising a protease cleavage domain of the predetermined protease, wherein the protease cleavage domain comprises a cleavage site for a caspase, wherein the linker sequence comprises spacers in between the repressor or reporter and protease cleavage site. The reference discloses a chimeric protein comprising CLBDG6 (CD4 trans-membrane domain) linked to the transcription factor domain through a linker sequence comprising a caspase cleavage site and a spacer. The CLBDG6 acts as a repressor of the transcription domain by translocating it to the cell membrane as opposed to its biological function in the nucleus as a transcription factor wherein the a cleavage by a protease such as the caspase releases it from the membrane and allows it to function normally as a transcription factor (see the entire document, specifically figures 1-2). Thus Hawkins et al. anticipate claims 1, 4-5 as written.

Claims 1, 4-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Xu et al. (Nucleic Acids Res., Apr 15 1998, Vol. 26(8):2034-2035). This rejection is based upon the public availability of a printed publication before the filing date of the instant application. Claims

1 and 4-5 of the instant application are drawn to a chimeric protein for detecting the presence of predetermined protease, comprising a repressor domain which represses the activity of a normally biologically active protein fused thereto as a reporter domain having a detectable activity when not fused to the repressor domain, both of which are linked together through a linking sequence comprising a protease cleavage domain of the predetermined protease, wherein the protease cleavage domain comprises a cleavage site for a caspase, wherein the linker sequence comprises spacers in between the repressor or reporter and protease cleavage site. Xu et al. disclose an identical chimeric protein comprising a repressor domain which represses the activity of a normally biologically active protein fused thereto as a reporter domain having a detectable activity when not fused to the repressor domain, both of which are linked together through a linking sequence comprising a protease cleavage domain of the predetermined protease, wherein the protease cleavage domain comprises a cleavage site for a caspase, wherein the linker sequence comprises spacers in between the repressor or reporter and protease cleavage site. The reference discloses a chimeric protein comprising the green fluorescent protein (GFP) and the blue fluorescent protein (BFP) linked together through a linker comprising a spacer and a caspase cleavage sequence. The two fluorescent proteins both act as reporters and repressors of each other. The placement of the two fluorescent proteins in close proximity reduces the fluorescence intensity compared to the intensity of the individual proteins. The cleavage by the predetermined protease such as a caspase eliminates the reduction in fluorescence. Thus Xu et al. anticipate claims 1, 4-5 as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-3 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al. or Hawkins et al. as applied to claims 1, 4-5 above, and further in view of Mattioni et al. (Methods in Cell Biol., Vol. 43:335-352, 1994). Claims 2-3 and 9 are specifically drawn to a fusion protein comprising a ß-glucuronidase and a hormone binding domain (HBD) linked through a predetermined protease cleavage site or sequence, wherein the ß-glucuronidase remains inactive as long as it is fused to HBD but is rendered active upon cleavage by said protease such that it is free from HBD.

The references of Xu et al. and Hawkins et al. which teach fusion proteins comprising a reporter and a repressor domain linked through a protease cleavage sequence has been discussed above. However, both references do not teach a fusion protein comprising a HBD wherein the reporter part of the fusion protein is rendered inactive because of its fusion to the HBD or that the reporter is rendered active upon cleavage of the HBD by a protease.

Mattioni et al. teach regulation of protein activities by fusion to steroid binding domains. The reference teaches that an alternate method to inducible expression of a protein activity can be developed by making fusion protein, comprising the protein of interest whose activity needs to be controlled (i.e., reporter domain), and a HBD sequence linked at the N-terminal or C-terminal of the reporter protein. The reference teaches that natural ligands of the HBDs in the

cell bind to the HBDs and create a steric hindrance which renders the reporter inactive. The reference also teaches that the common HBD used is that of the example of Glucocorticoid receptor (GR), which is ubiquitously expressed in mammalian cells. The reference teaches that HSP90 binds to the GR-HBD and creates a steric hindrance which renders any protein fused to it inactive. The reference teaches that the reporter can be activated by adding alternative ligands for the HBDs which will not inactivate the reporter protein and thereby the reporter activity can be modulated. However, this reference does not teach the use of a protease cleavage site between the HBD and reporter and the use of a protease in order to activate the reporter.

With the above references in hand it would have been obvious to one of ordinary skill in the art to combine the teachings and arrive at a fusion protein comprising a reporter such as ß-glucuronidase or any enzyme of interest and the HBD such as the GR-HBD linked through a predetermined protease cleavage site such as that of a specific caspase and use it to determine the presence of said protease. One of ordinary skill in the art would have been motivated to do so as Mattioni et al. provide a easy but yet robust method of modulating the activity of a protein and Xu et al. or Hawkins et al. teach the method of using fusion protein comprising protease cleavage sites for determining the presence of specific protease. One of ordinary skill in the art would have a reasonable expectation of success since all the above reference teach all the important aspects of the invention and one of skill in the art needs to just put them together.

Therefore, the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al. or Hawkins et al. as applied to claims 1, 4-5 above, and further in view of the common knowledge in the art. Claim 6-8 in this instant application are drawn to chimeric proteins for detecting the presence of predetermined protease, comprising a plurality of reporter or repressor domains or cleavage sites, wherein the repressor domain which represses the activity of a normally biologically active protein fused thereto as a reporter domain having a detectable activity when not fused to the repressor domain, both of which are linked together through a linking sequence comprising a protease cleavage domain of the predetermined protease, wherein the protease cleavage domain comprises a cleavage site for a caspase, wherein the linker sequence comprises spacers in between the repressor or reporter and protease cleavage site.

The reference of Xu et al. and Hawkins et al. as it applies to chimeric proteins comprising single reporter and repressor and cleavage sites have been discussed above. Using the teachings of the above references it would have been obvious to those skilled in the art to have multiple domains such that the signal intensity obtained for the reporter domain, whether it is fluorescence as in Xu et al. reference or the transcription of a detector gene as in the case of Hawkins et al. would be more intense and its detection be easier. Because of the simplicity and ease of use of the technique it would have also been obvious to one of ordinary skill in the art to use multiple protease cleavage sites and detect the presence of multiple set of proteases. One of ordinary skill in the art would have been motivated to do so as Xu et al. and Hawkins et al. disclose a robust but at the same time quite simple method for detecting a single type of protease using a chimeric protein comprising a single reporter, a single repressor and a single protease cleavage site.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Manjunath N. Rao Ph.D.
Patent Examiner, A.U. 1652
9/2/03

MANJUNATH RAO
PATENT EXAMINER